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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/273,217	03/19/1999	XIN-YUN HUANG	19603/1451(C	6809

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/273,217	XIN-YUN HUANG
Examiner	**Art Unit**
Nirmal S. Basi	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 17, 2001* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4, 6-22, and 24-35* is/are pending in the application.

4a) Of the above, claim(s) *10-18 and 28-35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 6-9, 19-22, and 24-27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 14
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Amendment filed 9/17/01 has been entered. Applicant has canceled claims 5 and 23 and amended claims 1 and 19.

Claim Rejection, 35 U.S.C. 112, second paragraph

2. The rejection of Amended claims 1 and 19 is maintained over old claims rejected in paper number 13 (9/17/01) under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection of claim 20 is maintained for reasons of record (paper number 13). Claims 2-4, 21-22 and 24-27 are rejected for depending on an indefinite base or intermediate claim

The rejection of amended claims 1 and 19 is maintained over old claims rejected in paper number 13 (9/17/01). Applicant argues the phrase "external vestibule" is defined on page 8 of the specification as being a portion of the ion channel located between the S5 transmembrane and pore forming region of the channel protein or between the pore forming region and the S6 transmembrane of the channel protein. Further Applicant argues the paragraph bridging pages 11 and 12 of the present application refers to variations of an "external vestibule portion". Applicant arguments have been fully considered but not found persuasive. The name "external vestibule portion" has not been clearly defined in the claims and specification so as to allow the metes and bounds of the claims to be determined. On page 8 the specification discloses, "Preferably, the portion of the ion channel to be blocked is the external vestibule. Most preferably, the external vestibule portion is located between the S5 transmembrane and the pore forming region of the channel protein or between the

pore". The specification on the paragraph bridging pages 11 and 12 of the present application discloses, "The vestibule portions of the ion channel listed herein include sequences which are substantially the same as the sequences listed herein. Variations, may be made, for example, the deletions or addition of amino acids that have minimal influence on the properties, structure, or nature of the amino acid", the paragraph further refers to the general nature of the variations. The term "external vestibule portion" has been defined only in general terms and is not clear if it encompasses portions of amino acid sequence outside the S5 transmembrane and the pore forming region of the channel protein, what particular amino acids determine it to being a "external vestibule portion", when is sequence "substantially the same as the sequences listed herein" as compared to when it is not "substantially the same as the sequences listed herein", what is the "minimal influence" that can be exerted and what property does it apply to, so as to allow the metes and bounds of the claims to be determined. Therefore, name "external vestibule portion" does not sufficiently serve to characterize said portion or the channel protein it encompasses. In conclusion the term the specification does not clearly state what the "external vestibule portion" is but only states, "**Preferably**, the portion of the ion channel to be blocked is". The word "preferably" does not define "external vestibule portion" but only encompasses one embodiment. The references cited by Applicant also do not clearly define the metes and bounds of the term "external vestibule portion". The description of Aiyer that the "ion conduction pathway, bounds at its external and internal entrances by wide vestibules, is formed in large part by the P-region and the C-terminal half

of S6" does not clearly define what exactly is encompassed by "external vestibule portion". For example what part of the P-region constitutes the "external vestibule portion".

Claim 20 remains indefinite because it is not clear what is the "binding portion" a portion of, so as to allow the metes and bounds of the claims to be determined. Applicant has not addressed Examiners previous rejection pertaining to "binding portion" therefore the claim remains indefinite.

Claims 6-9 are newly rejected for depending on a canceled base claim. Claim 6 recites the limitation "claim 5" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 7 is dependent on claim 6, claim 8 is dependent on claim 7 and claim 9 is dependent on claim 8.

Claims 2-4, 21-22 and 24-27 are rejected for depending on an indefinite base or intermediate claim and fail to resolve the issues raised above.

Claim Rejections, 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

3. The rejection of claims 1-8 and 19-26 is withdrawn under 35 U.S.C. 102(e) as being anticipated by Chandy et al (Ref A) in view of Applicants Amendments and arguments filed in paper number 15.

4. The rejection of Amended claims 1-2, 19-22, and 24 is maintained over old claims rejected in paper number 13 (9/17/01), under 35 U.S.C. 102(e) as being anticipated by Kem at al (Ref B). Applicant argues Kem et al use toxins to interact with the P region of voltage gated potassium channels which is a short stretch of amino acids between 5th and 6th transmembrane segments, by contrast, the claimed invention calls for evaluating whether a particular material "binds to the external vestibule portion of the ion channel". Applicants arguments have been fully considered but not found persuasive. As indicated in the rejection under 112, second paragraph the metes and bounds of the external vestibule portion have not been defined, and absent evidence to the contrary encompass the segment of the ion channel evaluated by Kem et al. The references cited by Applicant Aiyer, to support the definition of external vestibule portion discloses "ion conduction pathway, bounds at its external and internal entrances by wide vestibules, is formed in large part by the P-region and the C-terminal half of S6". The external loop between S5 and S6 which contains at least part of the dendrotoxin receptor and the short stretch of amino acids, the P-region, located between the fifth and sixth transmembrane segments, which were evaluated for channel activity are considered by Examiner to constitute the external vestibule portion, when read in light of the specification.

5. The rejection of Amended claims 1-2 and 19-22 and 24-25 is maintained over old claims rejected in paper number 13 (9/17/01) under 35 U.S.C. 102(b) as being anticipated by Stuhmer et al (Ref C). Applicant argues, "Nowhere does Stuhmer teach a method of identifying an ion channel blocker for an ion channel by "identifying, as an ion channel blocker for an ion channel, an antibody, binding portion of an antibody, probe, or ligand which antibody, binding portion of the antibody, probe, or ligand binds to the external vestibule portion of the on channel and is effective to inhibit ion transport through the ion channel". Applicants arguments have been fully considered but not found persuasive. Stuhmer et al disclose isolation of a family potassium channels (RCK 1, RCK 3, RCK 4 and RCK 5) from rat cortex and characterization of the channels expressed in Xenopus laevis oocytes following microinjection RCK-specific RNAs (see Abstract and Results). Also disclosed are transmembrane segments, S1 to S6, and the external vestibule portion, amino acids 356-360 of RCK 4 and RCK 5 (Fig. 2), are 100% identical to SEQ ID NO:1 of instant application. A profile of the pharmacological sensitivity of different RCK channels to K channel blockers 4-aminopyridine (4-AP) and tetraethylammonium (TEA) and several basic toxins was determined (Table 4). The results suggest that the reduced DTX sensitivity of Shaker, RCK3 and RCK4 channels may be due to a replacement of Asp 354 of RCK 5 in the S5-S6 bend region (**external vestibule portion**) by uncharged amino acids page 3242, column 1, last paragraph). The evaluation of binding of K channel blockers 4-aminopyridine (4-AP) and tetraethylammonium (TEA) and several basic toxins (probes) to S5-S6 bend region teach a method of identifying an ion

channel blocker for an ion channel by identifying, as an ion channel blocker which binds to the external vestibule portion of the on channel.

Claim Rejections, 35 U.S.C. 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Amended claims 1-4, 7-9, 19-22 and 24-27 is maintained over old claims rejected in paper number 13 (9/17/01), under 35 U.S.C. 103(a) as being unpatentable over Kem et al. (Ref.B) in view of Chandy et al (A) and further in view of Chandy et al (D), Stuhmer et al (C), Yatani et al (see IDS), Vassiliv et al (see IDS), Tejedor et al (E).

Applicant argues Nowhere does the Candy reference teach a method of identifying an ion channel blocker for an ion channel by identifying an ion channel blocker which binds to the external vestibule. Applicant argues Yatani describes monoclonal antibody that binds to G-protein, unrelated to voltage-gated potassium channel and the antibodies of Vassiliv are between transmembrane domains III and IV, this segment is different to the outer vestibule portion. Applicant argues Tejedor discloses the covalent attachment of alpha-scorpion toxin to an extracellular loop between transmembrane helices S5 and S6 and that said segments contain not only the external vestibule

region but also the P-region. Applicants arguments have been fully considered but not found persuasive. The references in combination taught the concept of identifying ion channel blockers for ion channel proteins and further in combination taught the concept of using probes or antibodies which could be targeted to the external vestibule of an ion channel. The references of Yatani and Vassiliv teach the use of antibodies in screening assays. The references of Kem, Chandy, Stuhmer, and Tejedor teach the concept of targeting ion channel for ion cannel blockers and encompass targeting the external vestibule. The teachings of Kem, Chandy, Stuhmer, Yatani, Vassiliv, Tejedor are disclosed in paper number 13.

As indicated in the rejection under 112, second paragraph the metes and bounds of the external vestibule portion have not been defined, and absent evidence to the contrary encompass the segment of the ion channel evaluated by Kem et al. The references cited by Applicant Aiyer, to support the definition of external vestibule portion discloses "ion conduction pathway, bounds at its external and internal entrances by wide vestibules, is formed in large part by the P-region and the C-terminal half of S6". The external loop between S5 and S6 which contains at least part of the dendrotoxin receptor and the short stretch of amino acids, the P-region, located between the fifth and sixth transmembrane segments, which were evaluated for channel activity are considered by Examiner to constitute the external vestibule portion, when read in light of the specification.

The evaluation, by Stuhmer, of binding of K channel blockers 4-aminopyridine (4-AP) and tetraethylammonium (TEA) and several basic toxins (probes) to S5-S6 bend region teach a method

of identifying an ion channel blocker for an ion channel by identifying, as an ion channel blocker which binds to the external vestibule portion of the on channel.

Tejedor et al disclose the use of antibodies raised against the "external vestibule portion" of the α subunit of sodium channel in determining α-scorpion toxin modification of sodium channel. Tejedor et al state, "The α-scorpion toxins modify sodium channel properties from the extracellular surface of the channel", and, "Therefore , our results provide direct evidence that at least a portion of the segment of α subunit located between amino acid residues 355 and 378 is extracellular as illustrated in Fig. 2". It is proposed that a portion for α-scorpion toxin is formed by peptide segment(s) between amino acid residues 355 and 378 which is located in an extracellular loop between transmembrane helices S5 and S6 of homologous domain I of the sodium channel α subunit (Abstract), i.e. "external vestibule portion".

The references of Kem, Chandy, Stuhmer, Yatani, Vassiliv and Tejedor teach: a) Assays for screening or methods of identifying ion channel blockers are known in the art; b) "external vestibule portion" of channel proteins is known in the art and has been used in methods to identify and screen ion channel blockers; c) antibodies are routinely used to screen ion channel function and d) antibodies to "external vestibule portion" of ion channels are known in the art .

The rejection of claims 1-4, 6-9, 19-22 and 24-27 is maintained for reasons of record in paper number 13, and reiterated below to show the proper combination of references which form the basis for the rejected claims. Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the method of identifying ion channel

blockers or method for screening a drug as an ion channel blocker, wherein the ion channel has an "external vestibule portion", by contacting a cell having an ion channel with an ion channel blocker candidate, and evaluating the cell to determine if the ion channel blocker binds to the external vestibule portion of the ion channel and inhibits ion channel transport through the ion channel by using the method of Kem et al or Chandy et al., by incorporating the ion channel comprising polypeptide of SEQ ID NO:1, as disclosed by Stuhmer et al or Chandy et al (Science) , for delineation of the spatial organization of the residues in the "external vestibule portion" to define the structure of ion channel conduction pathway and understanding the mechanism of ion permeation or screening for ion channel blockers wherein the ion channel blocker is an antibody as disclosed by Yatani et or Vassiliv et al. , or a ligand as disclosed by Kem et al. The ordinary artisan would have been motivated to use the method of Kem et al or Chandy et incorporating the ion channel "external vestibule portion" comprising SEQ ID NO:1, as disclosed by Stuhmer et al or Candy et al (Science), and use ion channel blockers which are ligands or antibodies in said method because Kem et al disclose "Mutations in the P-region dramatically alter ShK blocking affinities, consistent with the toxins interaction with residues in the external vestibule", (column 58, lines 52-57) and K channel blockers are useful "as "molecular calipers" for measuring distances between K channel amino acid residues in the outer vestibule of these channels", (column 2, lines 44-50). Further, the ordinary artisan would have been motivated use antibody as ion channel blockers because antibodies are known in the art for the "external vestibule portion" of the ion channels, or can be easily produced from known "external vestibule portion" of ion channels by standard methods

in the art, and further said antibodies are routinely used in the methods disclosed above as shown by Chandy et al, Tejedor et al, Yatani et al and Vassiliv et al.

The ordinary artisan would have expected success at using the above mentioned method for method of identifying ion channel blockers or method for screening a drug as an ion channel blocker, wherein the ion channel has an "external vestibule portion", because Kem et al, as well as others , have shown the importance of the "external vestibule portion" of an ion channel a key target for compounds showing a degree of similarity to the ShK pharamacophore and said compounds can be tested for K-channel binding, and those having binding affinity constitute valuable new leads, which may be further modified with the aim of improving binding affinity and channel sub-type specificity (column 28, paragraph 4). Further, since antibodies can be specifically targeted to the "external vestibule portion" of ion channels, they too would constitute as compounds that could be tested for K-channel binding, the specificity of the antibody-induced modification of ion currents can be tested by using peptides to block the immunoreactivity of the antibody, as is the case for antibody-induced modification of N^+ currents disclosed by Vassiliv et al.

7. A complete response to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) MPEP § 821.01.

8. No claim is allowed.

9. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
December 3, 2001

Yvonne Eyler
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